Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1(Previously presented). A conjugate of (1) at least one therapeutic agent for joint diseases and (2) hyaluronic acid, a hyaluronic acid derivative or a salt thereof, wherein said at least one therapeutic agent for joint diseases covalently binds to the hyaluronic acid, the hyaluronic acid derivative or the salt thereof via a spacer.

Claim 2 (Cancelled).

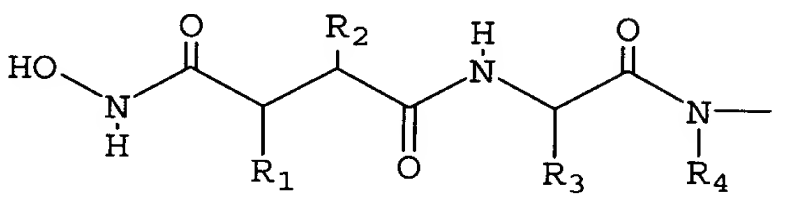
3(Previously presented). The conjugate of claim 1, wherein the therapeutic agent for joint diseases is a matrix metalloprotease inhibitor.

Claim 4 (Cancelled).

5(Previously presented). The conjugate of claim 3, wherein the weight ratio of the matrix metalloprotease inhibitor to the entire conjugate is 0.01 to 50%.

6(Previously presented). The conjugate of claim 3, wherein the matrix metalloprotease inhibitor is a hydroxamic acid residue.

7(Previously presented). The conjugate of claim 3, wherein the matrix metalloprotease inhibitor is a hydroxamic acid residue represented by the general formula (1):



(1)

wherein

R_1 is a hydrogen atom, a hydroxyl group or a straight-chain or branched-chain alkyl group having 1 to 8 carbon atoms;

R_2 is a straight-chain or branched-chain alkyl group having 1 to 8 carbon atoms;

R_3 is a straight chain or branched alkyl group having 1 to 8 carbon atoms which may be substituted with a cycloalkyl group, an aryl group or a heterocyclic group; and

R_4 is a hydrogen atom or an alkyl group having 1 to 4 carbon atoms.

8(Previously presented). The conjugate of claim 1, wherein the spacer is represented by the general formula (2):

$$-R_5-R_6-R_7-R_8- \qquad (2)$$

wherein

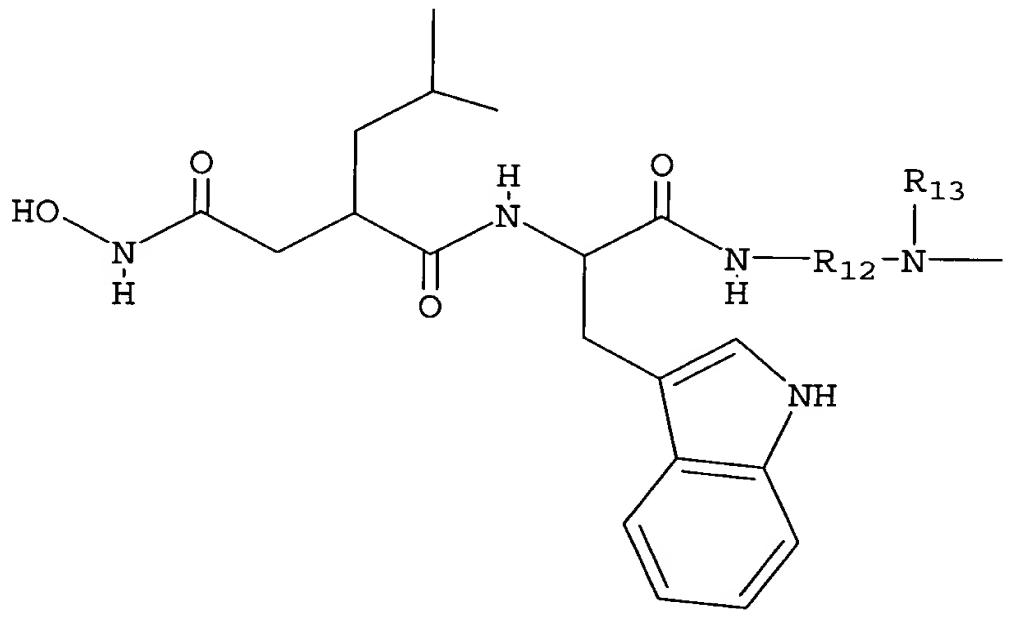
R_5 is a straight-chain or branched-chain alkylene group having 1 to 8 carbon atoms;

R_6 is an oxygen atom or a methylene or imino group which may be substituted with a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms;

R_7 is a straight-chain or branched-chain alkylene group having 1 to 10 carbon atoms into which one to three oxygen atoms may be inserted; and

R_8 is an oxygen atom, a sulfur atom or NR_9 wherein R_9 is a hydrogen atom or a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms.

9(Currently amended). The conjugate of claim [[1]] 3, wherein the matrix metalloprotease inhibitor and the spacer constitute a moiety represented by the general formula (3):



(3)

wherein

R_{12} is a straight-chain or branched-chain alkylene group having 2 to 23 carbon atoms into which one imino group and/or one to four oxygen atoms may be inserted; and

R_{13} is a hydrogen atom or a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms.

10(Previously presented). The conjugate of claim 3, wherein the matrix metalloprotease inhibitor in the form of a conjugate with hyaluronic acid, a hyaluronic acid derivative or a salt thereof inhibits a matrix metalloprotease *in situ*.

11(Previously presented). A method for preparing the conjugate of claim 1 comprising binding a site of the therapeutic agent for joint diseases that does not affect the activity of the agent to a carboxyl group, a hydroxyl group or a functional group at the reducing end of hyaluronic acid, a hyaluronic acid derivative or a salt thereof by direct chemical reaction or via a spacer.

12(Previously presented). A pharmaceutical composition comprising the conjugate of any one of claims 1, 3, 5-10, 18-21, 23 and 24 and a pharmaceutically acceptable diluent.

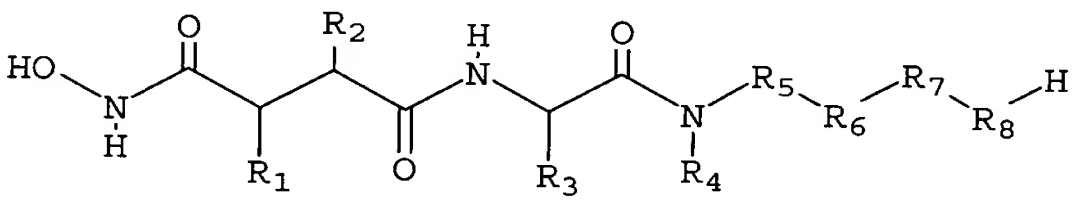
Claims 13-16 (Cancelled).

17(Previously presented). A method for treating a patient having a joint disease comprising administering a pharmaceutical composition containing a pharmaceutically effective amount of the conjugate of any one of claims 1, 3, 5-10, 18-21, 23 and 24 as the effective ingredient to the patient.

18(Previously presented). The conjugate of claim 1, wherein the therapeutic agent for joint diseases is selected from the group consisting of a cyclooxygenase 2 inhibitor, an antirheumatic agent and a matrix metalloprotease inhibitor.

19(Previously presented). The conjugate of claim 1, wherein the bond between at least one therapeutic agent for joint diseases and hyaluronic acid, a hyaluronic acid derivative or a salt thereof is selected from the group consisting of an amide bond, an ether bond and a sulfide bond.

20(Previously presented). A conjugate obtained by reacting a compound represented by the following general formula:



wherein

R_1 is a hydrogen atom, a hydroxyl group or a straight-chain or branched-chain alkyl group having 1 to 8 carbon atoms;

R_2 is a straight-chain or branched-chain alkyl group having 1 to 8 carbon atoms;

R_3 is a straight chain or branched alkyl group having 1 to 8 carbon atoms which may be substituted with a cycloalkyl group, an aryl group or a heterocyclic group;

R_4 is a hydrogen atom or an alkyl group having 1 to 4 carbon atoms;

R_5 is a straight-chain or branched-chain alkylene group having 1 to 8 carbon atoms;

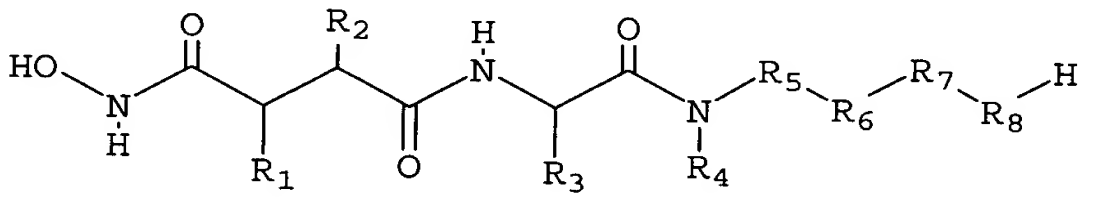
R_6 is an oxygen atom or a methylene or imino group which may be substituted with a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms;

R_7 is a straight-chain or branched-chain alkylene group having 1 to 10 carbon atoms into which one to three oxygen atoms may be inserted; and

R_8 is an oxygen atom, a sulfur atom or NR_9 wherein R_9 is a hydrogen atom or a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms;

with hyaluronic acid, a hyaluronic acid derivative or a salt thereof and a dehydrative condensation agent.

21(Previously presented). A conjugate according to claim 20 obtained by reacting a compound represented by the following general formula:



wherein

R_1 is a hydrogen atom, a hydroxyl group or a straight-chain or branched-chain alkyl group having 1 to 8 carbon atoms;

R_2 is a straight-chain or branched-chain alkyl group having 1 to 8 carbon atoms;

R_3 is a straight chain or branched alkyl group having 1 to 8 carbon atoms which may be substituted with a cycloalkyl group, an aryl group or a heterocyclic group;

R_4 is a hydrogen atom or an alkyl group having 1 to 4 carbon atoms;

R_5 is a straight-chain or branched-chain alkylene group having 1 to 8 carbon atoms;

R_6 is an oxygen atom or a methylene or imino group which may be substituted with a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms;

R_7 is a straight-chain or branched-chain alkylene group having 1 to 10 carbon atoms into which one to three oxygen atoms may be inserted; and

R_8 is an oxygen atom, a sulfur atom or NR_9 wherein R_9 is a hydrogen atom or a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms;

with hyaluronic acid, a hyaluronic acid derivative or a salt thereof, a dehydrative condensation agent and a reaction accelerating additive.

22(Previously presented). A method of treating a joint disease in a patient in need thereof, comprising administering a pharmaceutical composition to said patient in an amount sufficient for said treatment, wherein said pharmaceutical composition comprises a conjugate in accordance with claim 1.

23(Previously presented). The conjugate of claim 1, wherein component (1) is a single therapeutic agent for joint disease.

24(Previously presented). The conjugate of claim 1, wherein component (2) is hyaluronic acid or a salt thereof.

25(New). The method of claim 17, wherein the joint disease is selected from the group consisting of osteoarthritis, rheumatoid arthritis, and scapulohumeral periarthritis.